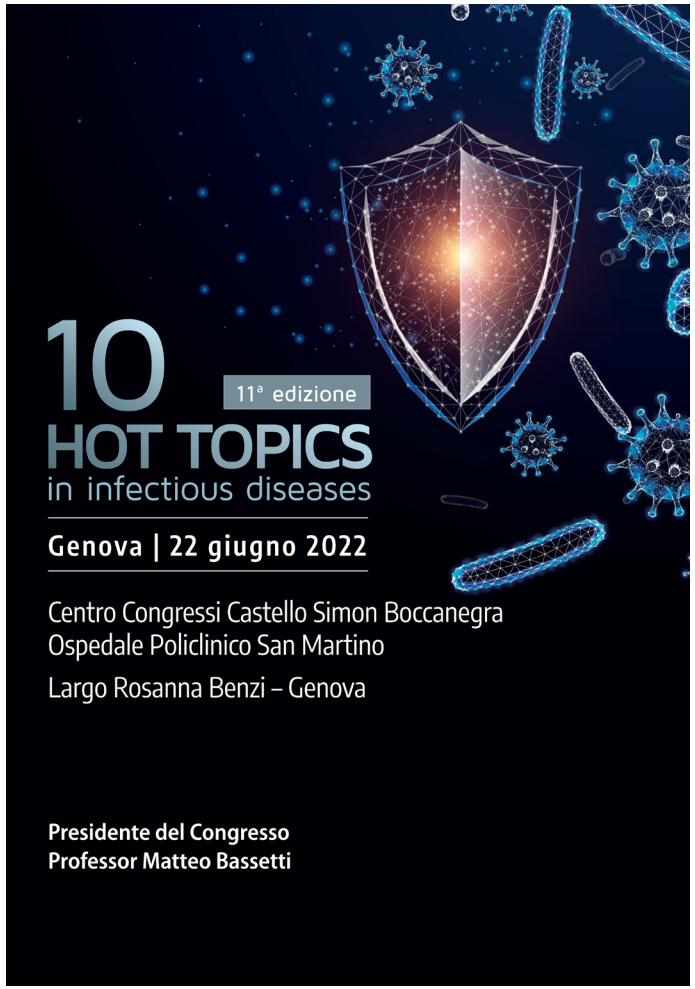

Come migliorare l'approccio alla terapia di *Staphylococcus aureus*

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Sistema Sanitario Regione Liguria
Istituto di Ricovero e Cura a Carattere Scientifico

Disclosures

Lecture fees and board meeting fees from:

- Gilead
- Janssen
- MSD
- Mundipharma
- Pfizer

None related to this presentation

Terapia di *Staphylococcus aureus*

- Oxacillin/nafcillin/ Cefazolin
- Vancomycin/teicoplanin
- Fosfomycin
- TMP-SMX
- Clindamycin

- Daptomycin
- Linezolid
- Tigecyclin

- Ceftaroline, ceftobiprole
- Tedizolid

Lipoglycopeptides

- Dalbavancin, oritavancin
- Telavancin
- FQ: Delafloxacin (nemonoxacin and zabofloxacin)
- Omadacycline - first-in-class aminomethylcycline (tetracycline) antibiotic, IV and oral, FDA approved for CAP and ABSSSI
- Lefamulin - semisynthetic pleuromutilin protein synthesis inhibitor, FDA approved for CAP

Terapia di *Staphylococcus aureus*

- Oxacillin/nafcillin/ Cefazolin
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- Fosfomycin
- TMP-SMX
- Clindamycin

- Daptomycin
- Linezolid
- Tigecyclin

- Ceftaroline, ceftobiprole
- Tedizolid

New agents:

All successfully studied in ABSSSI

Some in pneumonia (CAP, HAP)

Few studied and approved for BSI

acin and zabofloxacin)

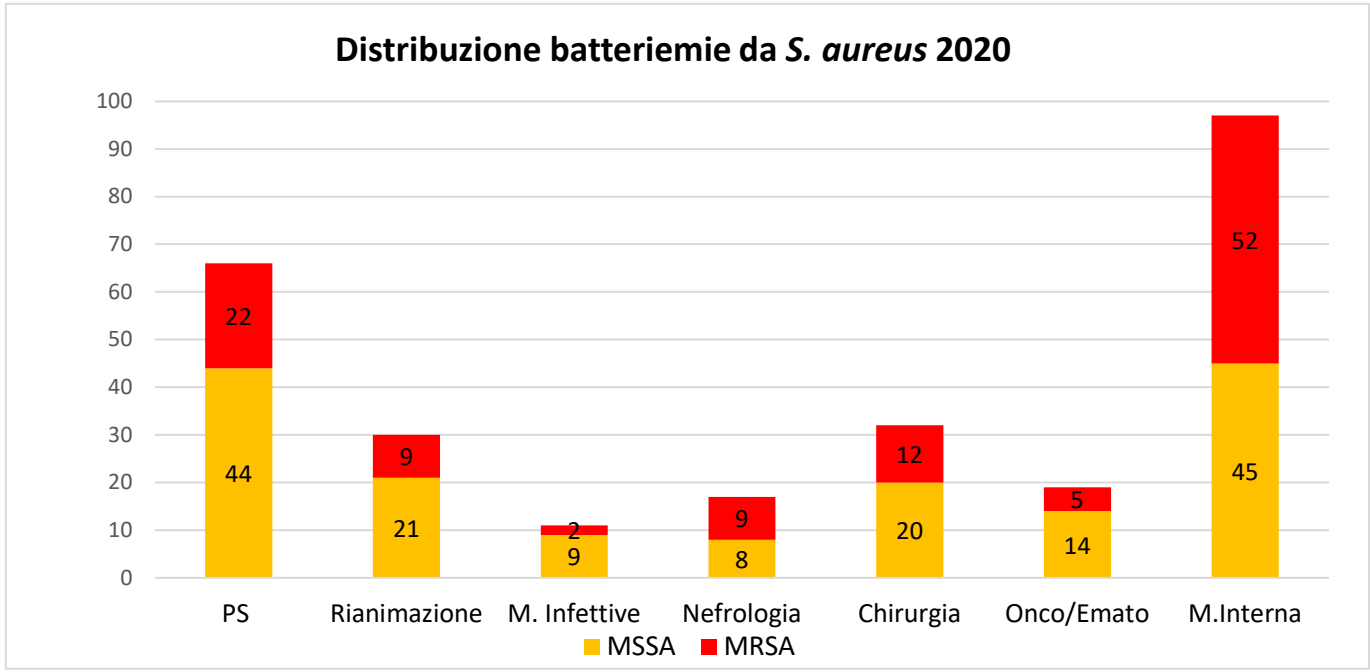
s aminomethylcycline
and oral, FDA approved

leuromutilin protein
roved for CAP

San Martino SAB 2020

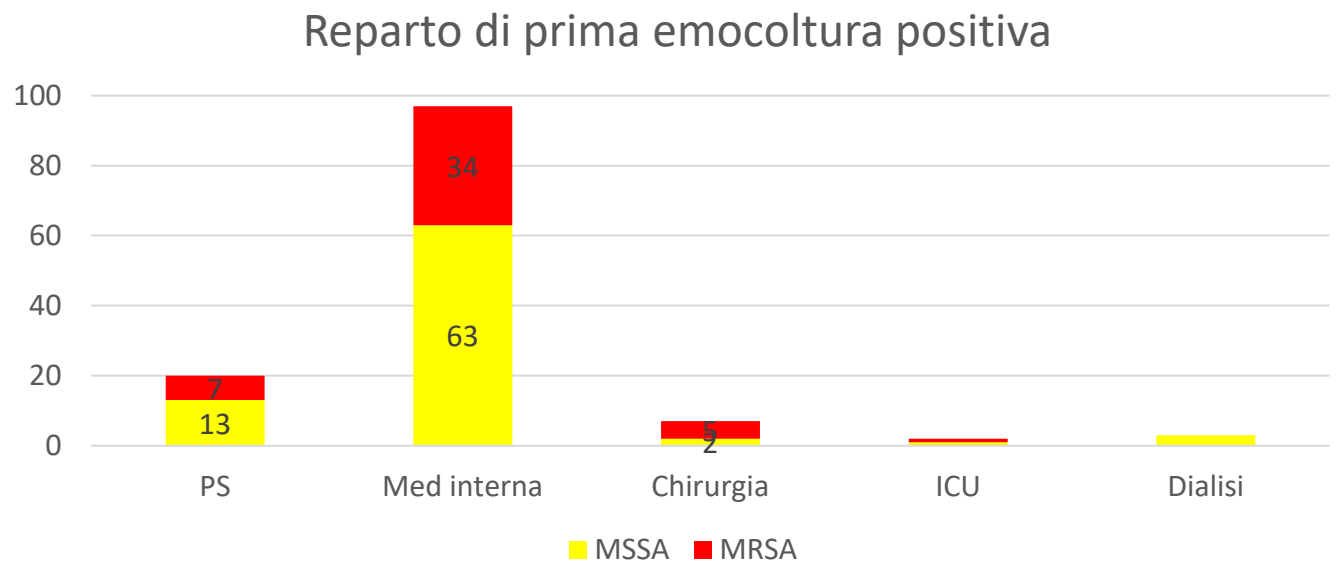
2020 - 275 SAB

- 111 (40.4%) MRSA BSI
- mediana di età 75 anni (IQR 64-83), 159 (57%) uomini



15/11/2021-30/04/2022 - 129 SAB in quasi 6 mesi

- 47 (36%) MRSA BSI
- mediana età 73 anni (range, 20-97), 76 (59%) uomini
- CA 27%, HCA 4%, **HA 69%**
- Dialisi, n=15 (12%) (10 MSSA)
- DM, n=41 (32%) (42% in MRSA BSI)
- CVC, n=60 (46%)



Systematic review and meta-analysis to estimate all-cause mortality in S. aureus BSI (SAB)

- Review of observational studies on patients with SAB: 01/01/1991 – 07/05/2021
- 341 studies were included, describing a total of 536,791 patients

- From 2011 onward, the estimated mortality was
  - 10.4% (95% CI, 9.0%-12.1%) at 7 days,
  - 13.3% (95% CI, 11.1%-15.8%) at 2 weeks,
  - 18.1% (95% CI, 16.3%-20.0%) at 1 month,
  - 27.0% (95% CI, 21.5%-33.3%) at 3 months,
  - 30.2% (95% CI, 22.4%-39.3%) at 1 year.
- In a meta-regression model of 1-month mortality, predictors of increased mortality were
  - MRSA SAB aOR: 1.04; 95% CI, 1.02-1.06 per 10% increase in MRSA proportion
  - Decade
  - Geographical location

Bai et al. Staphylococcus aureus bacteremia mortality across country income groups: A secondary analysis of a systematic review. CMI 2022

Systematic review and meta-analysis to estimate all-cause mortality in S. aureus BSI (SAB)

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  - 30.2% (95% CI, 22.4%-39.3%)at 1 year.

Mortalità	2021-2022	2019-2020, MRSA
7 giorni	16% (21/129)	
	MSSA 13% (11/82)	
	MRSA 21% (10/47)	
30 giorni	37% (38/129)	36.5% (61/167)
90 giorni		51.5% (86/167)

Bai AD, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. Clin Microbiol Infect. 2022 Mar 23:S1198-743X(22)00154-9.

Characteristics, median (IQR) in studies	Prior to 2001	2001 to 2010	2011 onwards
Mean age reported	58.8 (54.9, 63.3)	62.0 (58.3, 65.5)	**60.1 (57.7, 63.8)**
Mean Charlson comorbidity index	**2.75 (1.77, 4.48)**	**4.10 (3.20, 5.20)**	**4.70 (3.52, 4.94)**
Proportion with nosocomial infection	59% (46%, 84%)	49% (32%, 65%)	39% (27%, 63%)
Proportion with MRSA	30% (6%, 46%)	36% (21%, 51%)	34% (19%, 46%)
Proportion with line infection	28% (20%, 36%)	24% (17%, 35%)	19% (12%, 27%)
Proportion with osteoarticular infection	6% (3%, 9%)	11% (6%, 15%)	13% (7%, 19%)
Proportion with infective endocarditis	8% (4%, 11%)	7% (4%, 11%)	8% (5%, 11%)
Proportion with complicated SAB	48% (31%, 54%)	43% (27%, 58%)	59% (41%, 86%)
Proportion with ID consultation	34% (27%, 67%)	67% (50%, 80%)	76% (56%, 81%)
Proportion with echocardiography	41% (33%, 47%)	54% (46%, 70%)	61% (39%, 82%)

San Martino MRSA SAB:

Median Charlson Comorbidity Index (CCI) aggiustato per età 6 (IQR 5-7), 58% males, median age 78 (IQR 68 - 86)

Bai AD, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. Clin Microbiol Infect. 2022 Mar 23:S1198-743X(22)00154-9.

Clinical Infectious Diseases

MAJOR ARTICLE

Acute Myocardial Infarction and Community-acquired *Staphylococcus aureus* Bloodstream Infection: An Observational Cohort Study

John F. McNamara,[1,2] Patrick N. A. Harris,[1,3] Mark D. Chatfield,[1] and David L. Paterson[1,4]

[1]University of Queensland Centre for Clinical Research, Brisbane, Australia, [2]The Department of Infectious Diseases, The Prince Charles Hospital, Brisbane, Pathology Queensland, Australia, [3]Royal Brisbane and Women's Hospital, Herston, Australia, and [4]Department of Infectious Diseases, Royal Brisbane and Women's Hospital, Herston, QLD, Australia

- MI within 7 days from CA-SAB
  - 1.7% (89/5157) vs. 0.4% (37/15303)
  - OR 5 (95%CI 3.3-7.5) p>0.0001

Table 2. Multivariable Logistic Regression for Myocardial Infarction During 7-Day Risk Period Following Index Culture

Variable	Odds Ratio	95% Confidence Interval		*P*
CA-SABSI	5.0	3.3	7.5	<.0001
Male	1.0	.7	1.5	.90
Age group: reference, 20–44 years				
45–64	9.2	3.3	38.2	<.01
65–79	10.4	5.3	58.9	<.0001
Over 80	19.2	6.5	81.6	<.0001
Socioeconomic status: reference, IRSAD 1–2, lowest				
IRSAD 3–4	.7	.4	1.2	.20
IRSAD 5–6	.6	.3	1.0	.05
IRSAD 7–8	.6	.4	1.0	<.05
IRSAD 9–10, highest	.5	.2	1.0	.08

Data show the variables and associated risk of admission myocardial infarction following CA-SABSI during 7 days after culture collection. (n = 15 303). There were 89 and 37 admissions for myocardial infarction for CA-SABSI and culture-negative cases, respectively, during the 7-day time frame.

Abbreviations: CA-SABSI, community-acquired *Staphylococcus aureus* bloodstream infection; IRSAD, index of relative socioeconomic advantage and disadvantage.

McNamara et a. CID 2021

How to improve outcome in SAB?

- ID consult
  - Adherence to guidelines
  - Implementations of care bundles (diagnosis and treatment)
  - Improving the diagnosis of metastatic disease and endovascular infection

JAMA Network Open

Original Investigation | Infectious Diseases

Association of Infectious Diseases Consultation With Long-term Postdischarge Outcomes Among Patients With *Staphylococcus aureus* Bacteremia

Michihiko Goto, MD, MSCI; Michael P. Jones, PhD; Marin L. Schweizer, PhD; Daniel J. Livorsi, MD, MS; Eli N. Perencevich, MD, MS; Kelly Richardson, PhD; Brice F. Beck, MA; Bruce Alexander, PharmD; Michael E. Ohl, MD, MSPH

- 31 002 (97.6% men); median age 64 yrs, overall mortality 60.6%; SAB recurrence 15.4%
- 68% of deaths and 47.5% recurrences occurred more than 90 days after discharge
- 49.5% of patients received ID consultation during the index hospital stay
- ID consultation was associated with prolonged improvement in the composite outcome (aHR at 5 years, 0.71; 95%CI, 0.68-0.74; $P < .001$), and in mortality and recurrence rate separately

Lopez-Cortes LE, et al. Impact of an evidence-based bundle intervention in the quality-of-care management and outcome of Staphylococcus aureus bacteremia. Clin Infect Dis 2013; 57:1225±1233; Goto et al. JAMA Open 2020;3(2):e1921048

Better antibiotic therapy?

Early switch from vancomycin to daptomycin

- **Retrospective cohort study, MRSA SAB 2007-2014**
- 7411 patients received vancomycin for MRSA BSI
- 606 (8.2%) patients switched from vancomycin to daptomycin during the first hospitalization, in median on day 6
- Patients were younger and more likely to receive ID consult
- 108 (1.5%) switched from vancomycin to daptomycin within 3 days of starting vancomycin
- 30d mortality 17%

- In the multivariable analysis, switching to daptomycin within 3 days was significantly associated with lower 30-day mortality (HR 0.48; 95% CI: .25, .92)
  - 30d mortality 8% vs 17%
- However, switching to daptomycin at any time during the first hospitalization was not significantly associated with 30-day mortality (HR: 0.87; 95% CI: .69, 1.09)
  - 30d mortality 13% vs 17%

Schweizer ML, et al. Comparative Effectiveness of Switching to Daptomycin Versus Remaining on Vancomycin Among Patients With Methicillin-resistant Staphylococcus aureus (MRSA) Bloodstream Infections. Clin Infect Dis. 2021 Jan 29;72(Suppl 1):S68-S73.

Combination therapy

- The hope of benefit …

- Numerous observational, mainly retrospective, trials (with bias)
- Few RCT, usually not demonstrating benefit

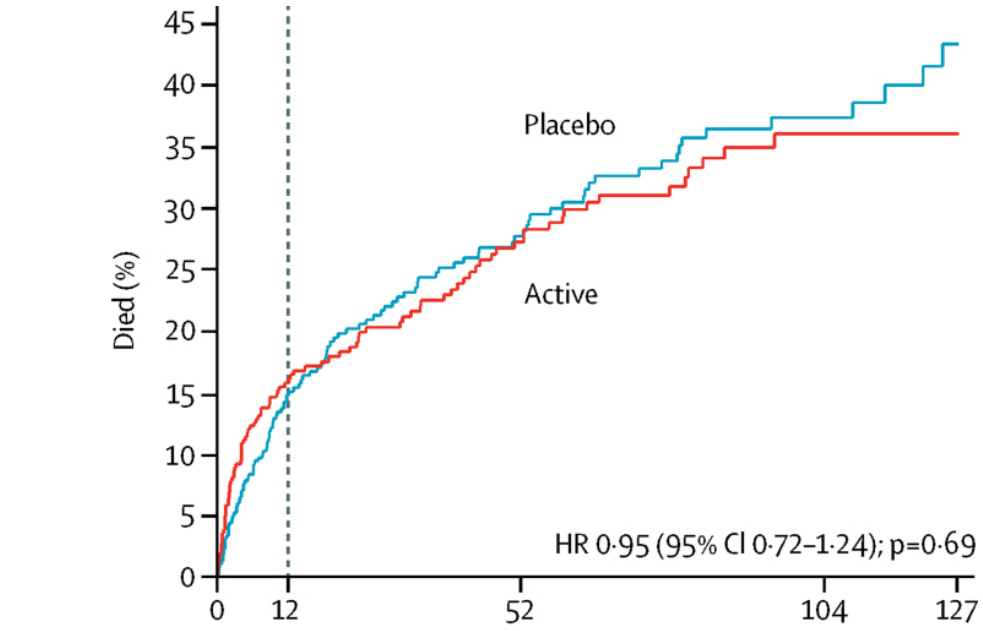
Combination therapy for MSSA – the largest RCT

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

- RCT, n=711
- MSSA (94%)
- 79% rifampicin dose 900mg/d
- Flucloxacillin as backbone 82%
- **CCI 2 (IQR 0-3)**

- No benefit of mortality and composite endpoint of mortality and failure

- Small but significant reduction in bacteriologically and clinically defined disease recurrences (4% vs 1%; 6% vs. 2%)



Number at risk (deaths)					
Placebo	388 (56)	302 (35)	161 (17)	55 (4)	29
Active	370 (56)	273 (27)	142 (13)	49 (0)	32

Thwaites et al. Lancet 2018 391: 668–78

Clinical Infectious Diseases
MAJOR ARTICLE

Combination treatment for MSSA – daptomycin?

Adjunctive Daptomycin in the Treatment of Methicillin-susceptible *Staphylococcus aureus* Bacteremia: A Randomized, Controlled Trial

Matthew P. Cheng,[1,a] Alexander Lawandi,[2,a,©] Guillaume Butler-Laporte,[2,a,©] Samuel De l'Étoile-Morel,[2] Katryn Paquette,[3] and Todd C. Lee[2,4,5]

- Randomized, double-blind, placebo-controlled trial in Canada (DASH study)
- Patients aged ≥18 years with MSSA BSI receiving either cefazolin or cloxacillin monotherapy were considered for inclusion
- In addition to the standard-of-care treatment, participants received a 5-day course of adjunctive daptomycin or placebo.
- The primary outcome was the duration of MSSA BSI in days

Results:

- 318 participants screened, 115 were enrolled and 104 were included in the ITT, **CCI 5 (IQR 3-9)**
- The median duration of bacteremia was 2.04 days vs 1.65 days (P = .40)
- In mITT analysis that involved participants who remained bacteremic at the time of enrollment, median duration of bacteremia the same – 3 days
- 90d mortality 18.9% vs 17.7% in the placebo arm (p=1.0)

Cheng, M.P et al. Adjunctive Daptomycin in the Treatment of Methicillin-susceptible Staphylococcus aureus Bacteremia: A Randomized, Controlled Trial. Clin Infect Dis **2021**, 72, e196–e203

microorganisms

MDPI

Article

The Effectiveness of Combination Therapy for Treating Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Systematic Literature Review and a Meta-Analysis

Sara Grillo [1,†], Mireia Puig-Asensio [1,2,3,*,†], Marin L. Schweizer [3,4], Guillermo Cuervo [1,2], Isabel Oriol [5], Miquel Pujol [1,2] and Jordi Carratalà [1,2,6]

Combination therapy for MSSA, summary

- 12 studies (6 RCTS): combination therapy
- did not significantly reduce 30-day mortality (pRR 0.92, 95% CI, 0.70–1.20), 90-day mortality (pRR 0.89, 95% CI, 0.74–1.06), or any-time mortality (pRR 0.91, 95% CI, 0.76–1.08)
- Among patients with deep-seated infections, adjunctive rifampicin may reduce 90-day mortality (3 studies with moderate-high risk of bias; pRR 0.62, 95% CI, 0.42–0.92)
- For secondary outcomes, it decreased the risk of relapse (pRR 0.38, 95% CI, 0.22–0.66), but this benefit was not maintained when pooling RCTs (pRR 0.54, 95% CI, 0.12–2.51)
- Associated with an increased risk of adverse events (pRR 1.74, 95% CI, 1.31–2.31)

Grillo et. al Micoorganisms 2022

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia

A Randomized Clinical Trial

Combination treatment for MRSA - 1
Adding an anti-staphylococcal β-lactam

- Open-label, randomized clinical trial in 27 hospital sites in 4 countries from August 2015 to July 2018
- Included 352 hospitalized adults with MRSA BSI (1431 patients screened)
- Randomized to standard therapy (intravenous vancomycin (99%) or daptomycin) plus an anti-staphylococcal β-lactam (intravenous flucloxacillin, cloxacillin, or cefazolin (15.5%)) for 7 days (n = 174) or standard therapy alone (n = 178).
- Total duration of therapy was determined by treating clinicians and the β-lactam was administered for 7 days.
- The data and safety monitoring board recommended early termination of the study prior to enrolment of 440 patients because of safety and 352 patients randomized (mean age, 62.2 years), **CCI 5**
- The primary end point - 90-day composite of mortality, persistent bacteraemia at day 5, microbiological relapse, and microbiological treatment failure: 35% vs. 39%
- **No difference in 7/9 secondary endpoints**
  - **Persistent bacteremia at day 5: 11% vs 20%**
  - **Excluding patients receiving dialysis at baseline, AKI occurred in 34 of 145 (23%) vs 9 of 145 (6%)**

Conclusion: No significant improvement but higher nephrotoxity (potentially lower if cefazolin used in combination)

Tong et al. JAMA 2020 (CAMERA2)

Clinical Infectious Diseases
MAJOR ARTICLE

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Combination treatment for MRSA - 2
Adding fosfomycin to daptomycin

- **MRSA,** randomized (1:1) phase 3 superiority, open-label, and parallel group clinical trial dapto + fosfo (10 mg/kg of daptomycin intravenously daily plus 2 g of fosfomycin intravenously every 6 hours) vs daptomycin
- 155 patients completed the trial (674 screened 2013-2017), **CCI 3-4**
- Treatment success at TOC - 6 weeks after the end of therapy - 54.1% vs 42.0%; P = .135

Table 3. Reasons for Treatment Failure at Test of Cure

P Value[a]	Reason for Treatment Failure	Daptomycin Plus Fosfomycin, No. (%) of Patients (n = 74)	Daptomycin Alone, No. (%) of Patients (n = 81)	Proportion Difference (95% CI)
.133)	Treatment failure[b]	34 (45.9)	47 (58.0)	−12.1 (−27.7 to 3.6
to 10.9) .687	Mortality at TOC	18 (24.3)	22 (27.1)	−2.8 (−16.6
.8 to .4) .247[d]	Clinical failure[c]	0 (0.0)	3 (3.7)	−3.7 (−
18.0 to −4.3) .003[d]	Microbiological failure	0 (0.0)	9 (11.1)	−11.1 (−
.6 (2.8–22.5) .012	Any AE leading to treatment discontinuation	13 (17.6)	4 (4.9)	12
−11.3 (−23.2 to .6) .068	Additional antimicrobial therapy administered before TOC[e]	9 (12.1)	19 (23.4)	
5.9 (−2.6 to 14.4) .172	Lack of blood cultures at TOC	8 (10.8)	4 (4.9)	
−2.4 (−7.2 to 2.5) .622[d]	Loss to follow-up	1 (1.3)	3 (3.7)	

Pujol et al. Clin Infect Dis 2021;72(9):1517–25

Clinical Infectious Diseases
MAJOR ARTICLE

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Similar overall mortality: 18/74 (24%) vs. 22/81 (27%), p=0.9

Subgroup analysis:

- Benefit of combination if Pitt score > 1 and age < 74 yo
- No benefit in endocarditis (present in 11% of participants)

DAP + CPT - lack of high quality data

- Randomised controlled open label
- Preliminary data on 40 patients: combination (*n* = 17) vs. standard monotherapy (*n* = 23, vancomycin in 21)

- Unanticipated in-hospital mortality difference:

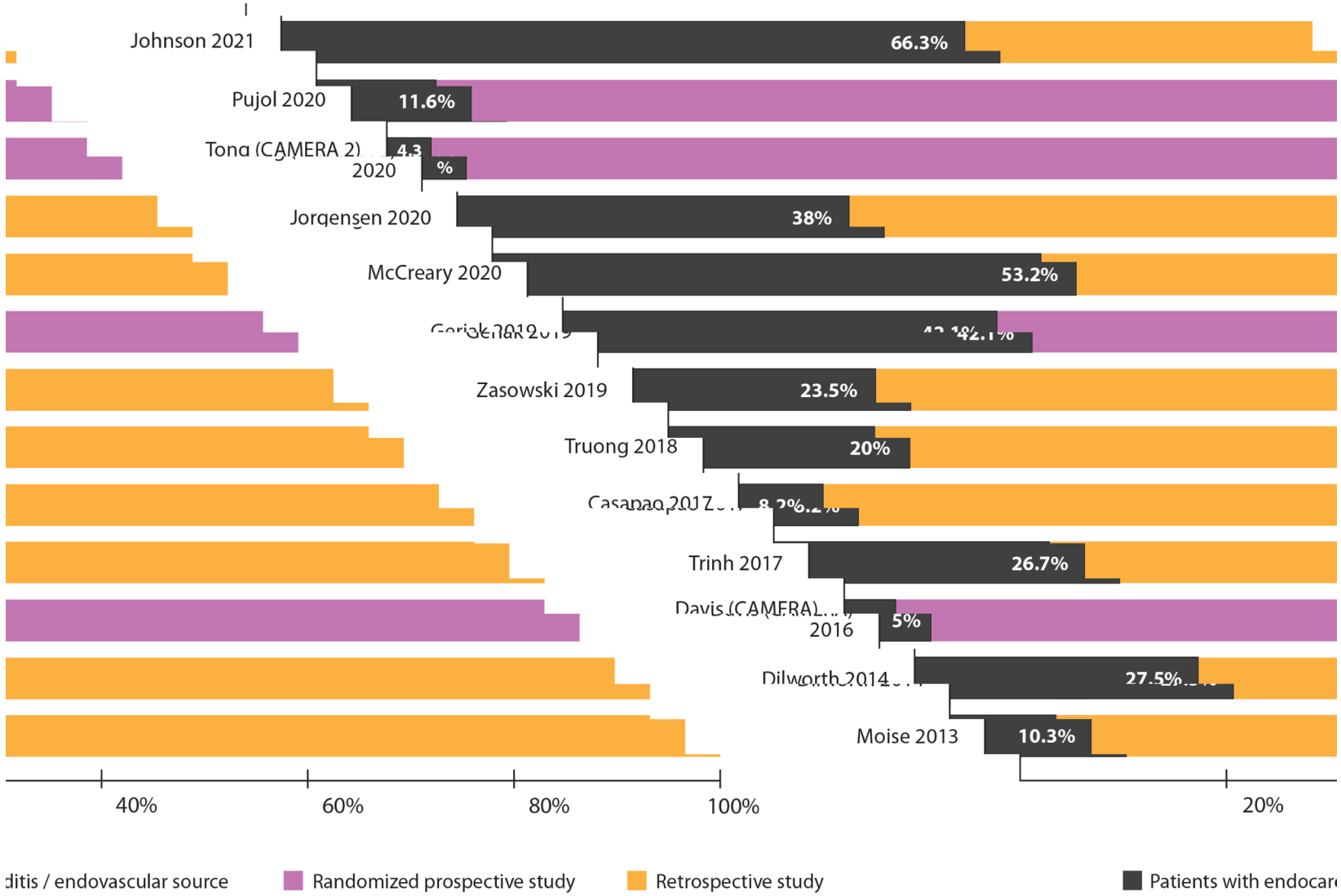
0% (0/17) vs. 26% (6/23), p= 0.029, causing us to halt the study

- No difference in the length of bacteremia…

Geriak AAC 2019;

- Retrospective, matched cohort study MRSA
- Patients receiving DAP-CPT for ≥72 hours at any point in therapy were matched to SOC, first by infection source, then age and renal function.
- SOC was empiric treatment with vancomycin or daptomycin and any subsequent combination antibiotic(s), except for DAP-CPT.
- **58 cases and 113 matched SOC (96% received vancomycin, and 56% escalated therapy at least once in the treatment course)**
- 30d mortality: 2 (8.3%) vs 14.2% (16/113) with SOC (p=NS)
  - The median MRSA BSI duration was 9.3 vs 4.8 days for DAP-CPT and SOC, respectively.
  - DAP-CPT was initiated on day 6 on average; after receipt of DAP-CPT, MRSA BSI duration was 3.3 days

McCreary Open forum ID 2020



arditis source of bacteremia among patients included in retrospective and prospective studies of MRSA combination therapy.
itibiotics for methicillin-resistant *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

Figure 3. Overview of endovascular/endoc
Abbreviations: CAMERA, combination sr

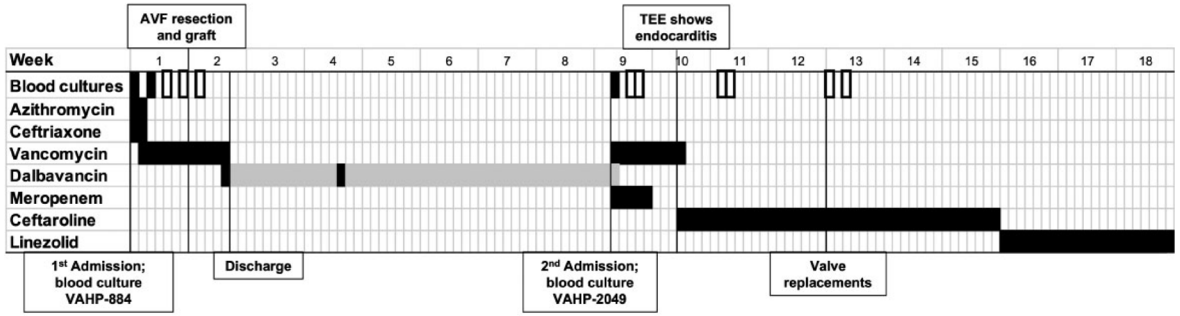
Rose et al. Clin Infect Dis 2021;73(12):2353–60

Clinical Infectious Diseases

BRIEF REPORT

Emergence of Dalbavancin, Vancomycin, and Daptomycin Nonsusceptible *Staphylococcus aureus* in a Patient Treated With Dalbavancin: Case Report and Isolate Characterization

Rutan Zhang,[1] Hari Polenakovik,[2,3] Ismael A. Barreras Beltran,[4] Adam Waalkes,[5]



Drug	VAHP-884	VAHP-2049
Vancomycin	1 mg/L (S)	4 mg/L (NS)
Vancomycin AUC ratio	0.6 (VSSA)	0.95 (hVISA/VISA)
Daptomycin	0.25 mg/L (S)	2 mg/L (NS)
Dalbavancin	0.003 mg/L (S)	0.5 mg/L (NS)
Nafcillin (PBP-NS)	4 mg/L (R)	1 mg/L (S*)
Meropenem (PBP1)	0.5 mg/L	0.25 mg/L
Ceftriaxone (PBP2)	16 mg/L	8 mg/L
Cephalexin (PBP3)	8 mg/L	8 mg/L
Cefoxitin (PBP4)	16 mg/L (R)	8 mg/L (R)
Ceftaroline (PBP2a)	0.5 mg/L (S)	0.25 mg/L (S)
Gene (NA; AA)	----	***walK*** (C1700T; Ala567Val)
	----	***scrA*** (C569T; Ala190Val)

Daptomycin resistance and non susceptibility

- Point mutations in *mprF* are the main cause of daptomycin treatment failure, mainly in MRSA strains
- Mechanism: altered cell membrane phospholipid profiles, enhanced positive surface charge, and changes in cell membrane fluidity
- the **"seesaw effect"** of distinct beta-lactams remains unclear (with potential mechanism of restoring susceptibility to beta-lactam antibiotics mediated by the *mprF* mutation and its impact on beta-lactam combination therapy)

Kang et al. 2017 Feb;55(2):153-15

Optimising the duration of antibiotic therapy?

Duration of therapy

- 14 days for uncomplicated
- 28-42 for complicated

- Predictors of complicated SAB (Fower Arch Intern Med 2003)
  - Prolonged (>48-72h) bacteremia
  - Fever > 72h after therapy onset
  - Community onset
  - Skin findings

  Definition of complicated:
  - IE excluded
  - No prostheses
  - BC negative on day 2-4
  - No fever > 72h after therapy onset
  - No evidence of metastatic infection

Liu IDSA CID 2011, Holland JAMA 2014; Cheng CID 2020

Length of treatment and 90d mortality in SAB

- Retrospective, single-center cohort study
- 225 patients with Uncomplicated SAB
- 305 patients with Complicated SAB
- 90-day mortality rates for duration of treatment: ≤14 days or >14 days

- In patients with Complicated SAB, >14 days associated with higher survival rate than ≤ 14 days
  - Duration of therapy (long vs. short) aHR 0.32 (95%CI 0.16-0.64) p=0.001
- Patients with Uncomplicated SAB exhibited no such improved survival when they received > 14 days
  - Duration of therapy (long vs. short) aHR 0.85 (95%CI 0.41-1.78) p=0.67

Abbas M, et al. Association between treatment duration and mortality or relapse in adult patients with Staphylococcus aureus bacteraemia: a retrospective cohort study. Clin Microbiol Infect. 2020 May;26(5):626-631. doi: 10.1016/j.cmi.2019.07.019.

Clinical Infectious Diseases
MAJOR ARTICLE

Comparable Outcomes of Short-Course and Prolonged-Course Therapy in Selected Cases of Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Pooled Cohort Study

Louise Thorlacius-Ussing,[1] Håkon Sandholdt,[1] Jette Nissen,[2] Jon Rasmussen,[3] Robert Skov,[4] Niels Frimodt-Møller,[5] Jenny Dahl Knudsen,[5] Christian Østergaard,[6] and Thomas Benfield[1]

[1]Center of Research and Disruption of Infectious Diseases, Department of Infectious Diseases, Copenhagen University Hospital–Amager and Hvidovre, Copenhagen, Denmark; [2]Department of Gynaecology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]Department of Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [4]Statens Serum Institut, Copenhagen, Denmark; [5]Department of Clinical Microbiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; and [6]Department of Clinical Microbiology, Copenhagen University Hospital–Amager and Hvidovre, Copenhagen, Denmark

Shortening the therapy

- Low risk MSSA SAB
- Retrospective, 6-10 vs 11-16 days
- 3 cohorts: 645, 219 and 141 patients
- Median treatment duration
  - Short course groups: 8 days (IQR, 7-10), 9 days (IQR, 8-10), and 8 days (IQR, 7-10).
  - Prolonged course groups: 14 days (IQR, 13-15), 14 days (IQR, 13-15), and 13 days (IQR, 12-15)
  - No significant differences in 90-day mortality

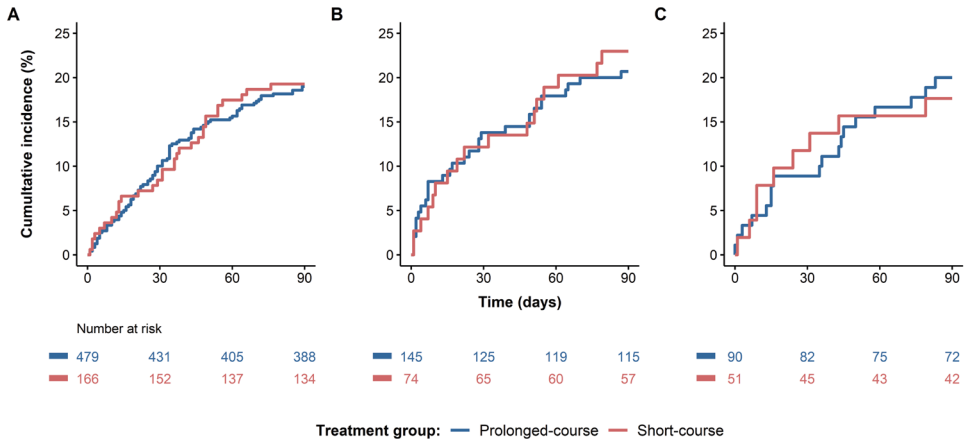


Figure 1. Absolute risk of 90-day mortality of patients with low-risk methicillin-susceptible *Staphylococcus aureus* bacteremia receiving short- or prolonged-course therapy in cohort I (*A*), cohort II (*B*), and cohort III (*C*).

Thorlacius-Ussing L, et al. Comparable Outcomes of Short-Course and Prolonged-Course Therapy in Selected Cases of Methicillin-Susceptible Staphylococcus aureus Bacteremia: A Pooled Cohort Study. Clin Infect Dis. 2021 Sep 7;73(5):866-872

Clinical Infectious Diseases
MAJOR ARTICLE

Comparable Outcomes of Short-Course and Prolonged-Course Therapy in Selected Cases of Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Pooled Cohort Study

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Shortening the therapy

- Duration of therapy was not associated with the risk of relapse

- Duration based on clinician's decision
- In the detailed cohort 1, patients with prolonged treatment course seemed sicker
  - higher CRP
  - more hospital acquired SAB
  - higher rate of TTE/TEE
  - fewer intravenous device-related infections
- Lack of data on some criteria of low risk SAB such as fever resolution within 72h, ecocardiography without evidence of endocarditis
- 90-day mortality 17-23% in 3 cohorts of these reportedly low risk patients
  - Simialar to mortality in all cases of SAB

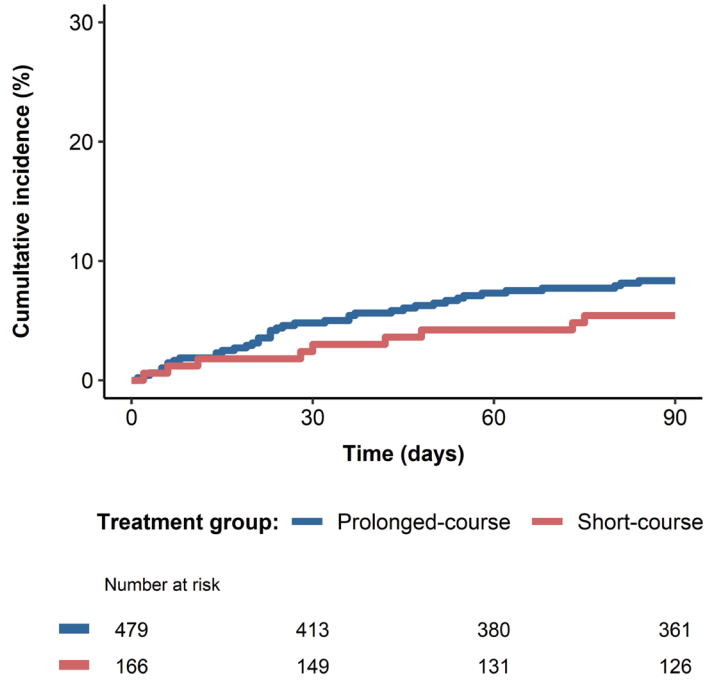

Figure 3. Cumulative incidence of 90-day relapse of patients with low-risk methicillin-susceptible *Staphylococcus aureus* bacteremia receiving short- or prolonged course therapy.

Thorlacius-Ussing L, et al. Comparable Outcomes of Short-Course and Prolonged-Course Therapy in Selected Cases of Methicillin-Susceptible Staphylococcus aureus Bacteremia: A Pooled Cohort Study. Clin Infect Dis. 2021 Sep 7;73(5):866-872.

Length of treatment - conclusions

- High risk of mortality
- Possibility of underestimation of complicated infection
  - in a RCT 32% patietns with no metastatic disease at enrollment had a final diagnosis of complicated bacteremia (Holland et al. JAMA 2018)
- Conservative approach to treatment duration

RCT:

- Thorlacius-Ussing L, et al. Efficacy of seven and fourteen days of antibiotic treatment in uncomplicated *Staphylococcus aureus* bacteremia (SAB7): study protocol for a randomized controlled trial. Trials **2019**; 20:250.
- Olmos C, et al. Short-course antibiotic regimen compared to conventional antibiotic treatment for gram-positive cocci infective endocarditis: randomized clinical trial (SATIE). BMC Infect Dis **2020**; 20:417.
- Ostergaard L, et al. Accelerated treatment of endocarditis—the POET II trial: rationale and design of a randomized controlled trial. Am Heart J **2020**; 227:40–6.

- No data and no planned RCT on HA MRSA SAB

Eichenberger EM, Fowler VG Jr, Holland TL. Duration of antibiotic therapy for Staphylococcus aureus bacteraemia: the long and the short of it. Clin Microbiol Infect. 2020 May;26(5):536-538. doi: 10.1016/j.cmi.2020.01.003

How to avoid underestimation of complicated infection?

- Endocarditis rate 10-20%
  - up to 25% (Rassmussen et al. Eur J Echocardiogrphy 2011)
  - Diagnose established at autopsy in 32% (Roeder Arch Intern Med 1999)
  - Up to 40% of *S. aureus* infective endocarditis occurs in patients without known predisposing risk factors for IE (Le Moing V Plos One 2015)

- Diagnosing complicated bacteremia
  - Use of scores for more targeted diagnosis of endocarditis
  - PET as a tool to detect metastatic infections (Thottacherry E, Cortés-Penfield NW. Clin Infect Dis. 2022)
  - Novel techniques: microbial Cell-Free DNA (Eichenberger EM, et al. Clin Infect Dis. 2022)
    - 66 patietns with SAB
    - Longer positivity: 15 days for mcfDNA vs 3 days for BC
    - Duration of Detection IAssociated With Metastatic Infection

Scores to predict the risk of IE, and thus the need for (TEE) echocardiography in SAB

Table 1. Overview of POSITIVE, PREDICT, and VIRSTA Scores

POSITIVE Cutoff: >4		PREDICT Cutoff: ≥2 (for Day 5 Score)		VIRSTA Cutoff: ≥3	
Item	Points Assigned	Item	Points Assigned	Item	Points Assigned
TTP <9 h	5	ICD	2	Cerebral or peripheral emboli	5
TTP 9–11 h	3	Permanent pacemaker	3	Meningitis	5
TTP 11–13 h	2	Community acquisition	2	Permanent intracardiac device or previous IE	4
IV drug use	3	Healthcare acquisition	1	Preexisting native valve disease[a]	3
Vascular phenomena[b]	6	Positive culture after 72 h	2	IV drug use	4
Predisposing heart disease[c]	5			Positive culture after 48 h	3
				Community or healthcare-associated bacteremia	2
				Severe sepsis or septic shock	1
				C-reactive protein >190 mg/L	1

Abbreviations: ICD, implantable cardioverter defibrillator; IV, intravenous; TTP, time to positivity.

[a]Any condition classified as medium or high risk by Dajani et al [25].

[b]Defined as arterial embolus, septic pulmonary embolus, mycotic aneurysm, intracranial bleeding, conjunctival hemorrhage, or Janeway lesions.

[c]Previous endocarditis, prosthetic heart valve, or any condition classified as medium or high risk [25].

van der Vaart et al. Clin Infect Dis 2022:74 (15 April)

PREDICT score

Quantifies the risk of IE and identifies patients who would most benefit most from undergoing TEE

Table 1. Calculation of PREDICT Score

	CIED			Onset of SAB			Prolonged Bacteremia ≥72 Hours	Total Risk Score
	ICD	PPM	Neither	Community	Healthcare	Nosocomial		
Day 1, points	2	3	0	2	1	0	…	Day 1 score ≥4: perform TEE now; <4: wait until day 5
Day 5, points	2	3	0	2	1	0	2	Day 5 score ≥2: Perform TEE; <2: no TEE

Abbreviations: CIED, cardiovascular implantable electronic device; ICD, implantable cardioverter defibrillator; PPM, permanent pacemaker; PREDICT, Predicting Risk of Endocarditis Using a Clinical Tool; SAB, *Staphylococcus aureus* bacteremia; TEE, transesophageal echocardiogram.

Need for echocardiography – the value of scores – study no. 1

- US study designed and prospectively conducted to validate the PREDICT scoring system
- 220 prospectively screened adults with SAB between January 2015 and March 2017
- 199 included and 23 (11.6%) diagnosed with definite IE within 12 weeks of initial presentation
- None of the patients with nosocomial SAB had IE, whereas 15 of 83 patients (18.1%) with community-acquired SAB had IE
- day 1 score of ≥4 had a sensitivity of 30.4% (TEE now) and a specificity of 93.8%
  - IE 39%
- day 5 score of ≤2 had a sensitivity and negative-predictive value of 100%
  - Score > 2 (no cardiac devices, non community onset) – IE 13%

- Additional factors such as surgery or invasive procedure in the past 30 days, prosthetic heart valve, and higher number of positive blood culture bottles in the first set of cultures were associated with increased risk of IE independent of the day 5 risk score

Abu Saleh O, Fida M, Asbury K, Narichania A, Sotello D, Bosch W, Vikram HR, Palraj R, Lahr B, Baddour LM, Sohail MR. Prospective Validation of PREDICT and Its Impact on the Transesophageal Echocardiography Use in Management of Staphylococcus aureus Bacteremia. Clin Infect Dis. 2021 Oct 5;73(7):e1745-e1753.

Need for echocardiography – the value of scores – study no. 2

- 922 Colombian patients with SAB 2012-2018
- 62 (6.7%) were diagnosed with IE
- The frequency of IE in patients with a negative VIRSTA score (<3) was 0.44% (2/454)
- The frequency of IE in patients with a negative PREDICT score on day 5 was 4.8% (30/622).
- Sensitivity and NPV
  - the VIRSTA score: 96.7% and 99.5%
  - the PREDICT score on day 5: 51.6% and 95.1%

  - Caveats: low rate of IE, low rate of intracardiac devices and prothesis but higher lever of CVC and HD

Peinado-Acevedo JS, et al. Validation of VIRSTA and Predicting Risk of Endocarditis Using a Clinical Tool (PREDICT) Scores to Determine the Priority of Echocardiography in Patients With Staphylococcus aureus Bacteremia. Clin Infect Dis. 2021 Sep 7;73(5):e1151-e1157. doi: 10.1093/cid/ciaa1844.

Need for echocardiography – the value of scores – study no. 3

- The Netherlands, 2017-2019
- 637 patients with SAB were screened, informed consent was obtained for 491 (77%); for the analysis of the risk scores, 14 patients who died within 48 hours of BC were excluded

- 477 SAB patients enrolled
  - 33% had community-acquired SAB,
  - 8% had a prosthetic valve,
  - 11% a cardiac implantable electronic device

- AIM: determine whether these 3 scores can be used to accurately classify a subset of patients with SAB as low risk for endocarditis, in whom TEE could be safely withheld without missing a diagnosis of IE

van der Vaart TW, Prinset al. Prediction Rules for Ruling Out Endocarditis in Patients With Staphylococcus aureus Bacteremia. Clin Infect Dis. 2022 Apr 28;74(8):1442-1449.

Need for echocardiography – the value of scores – study no. 3

- Echocardiography performed in 87% of patients, and 42% TEE
- Eighty-seven (18.2%) had definite endocarditis
- The PREDICT day 1 score (designed for early recognition of the patients with the highest risk of IE, who should undergo immediate TEE): high specificity (97%) and PPV (67%)

	Sensitivity	NPV	% of patients with SAB classified as at high risk for IE
POSITIVE (n = 362)	77.6% (65.8%-86.9%)	92.5% (87.9%-95.8%)	44.5%
PREDICT d5	85.1% (75.8%-91.8%)	94.5% (90.7%-97.0%)	50.7%
VIRSTA	98.9% (95.7%-100%)	**99.3% (94.9%-100%)**	70.9%

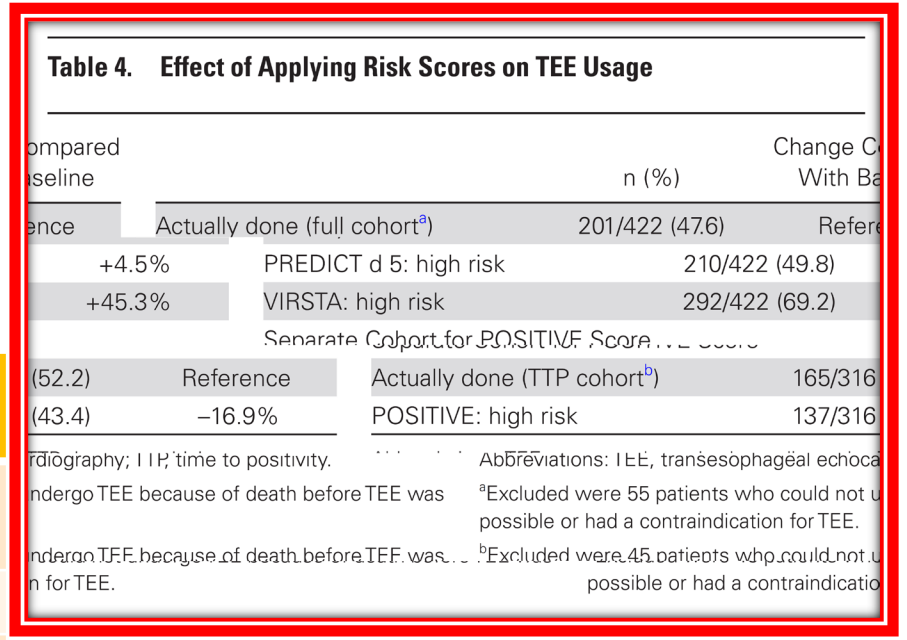

Table 4. Effect of Applying Risk Scores on TEE Usage

ompared seline		n (%)	Change C With Ba
ence	Actually done (full cohort[a])	201/422 (47.6)	Refere
+4.5%	PREDICT d 5: high risk	210/422 (49.8)	
+45.3%	VIRSTA: high risk	292/422 (69.2)	
	Separate Cohort for POSITIVE Score		
(52.2)	Reference	Actually done (TTP cohort[b])	165/316
(43.4)	−16.9%	POSITIVE: high risk	137/316

rdiography; TTP, time to positivity.

Abbreviations: TEE, transesophageal echoca

ndergo TEE because of death before TEE was

[a]Excluded were 55 patients who could not u possible or had a contraindication for TEE.

ndergo TEE because of death before TEE was

n for TEE.

[b]Excluded were 45 patients who could not u possible or had a contraindicatio

Conclusions: Only the VIRSTA score had an NPV of at least 98%, but at the expense of a high number of patients classified as high risk and thus requiring TEE

van der Vaart TW, Prinset al. Prediction Rules for Ruling Out Endocarditis in Patients With Staphylococcus aureus Bacteremia. Clin Infect Dis. 2022 Apr 28;74(8):1442-1449.

Come migliorare l'approccio alla terapia di *Staphylococcus aureus*

1. Rapid (>3 day of onset – max. with 24h from the results) start of optimal therapy
2. Use of combination treatment (daptomycin + ceftaroline/fosfomycin) in high risk (almost all?) patients
3. Active source control
4. Rapid diagnosis of IE (and surgery if needed) for at risk patients
5. Active and aggressive search for metastatic infection (PET)
6. Correct length of therapy, using also oral / long acting agents


Thank you for your attention